Inadequate anticoagulation by Vitamin K Antagonists is associated with Major Adverse Cardiovascular Events in patients with atrial fibrillation

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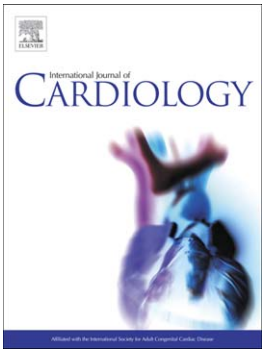

Inadequate anticoagulation by warfarin is associated with major adverse cardiovascular events in patients with atrial fibrillation

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INADEQUATE ANTICOAGULATION BY WARFARIN IS ASSOCIATED WITH MAJOR ADVERSE CARDIOVASCULAR EVENTS IN PATIENTS WITH ATRIAL FIBRILLATION

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Short title: Atrial fibrillation and Myocardial Infarction

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ABSTRACT

BACKGROUND: Time in therapeutic range (TTR) reflects the quality of anticoagulation and is inversely correlated with ischemic stroke in atrial fibrillation (AF) patients. Few data on the relationship between TTR and myocardial infarction (MI) are available. We investigated the association between TTR and Major Adverse Cardiovascular Events (MACE) in a cohort of anticoagulated AF patients.

METHODS: We calculated TTR for 627 AF patients on vitamin K antagonists, who were followed for a median of 30.8 months (1755 patients-year). The primary outcome was a combined endpoint of MACE including fatal/nonfatal MI and cardiovascular death.

RESULTS: Mean age was 73.3 (±8.2) years, and 40.2% were women. **During follow-up, we recorded 67 events: 19 stroke/TIA (1.1%/year) and 48 MACE (2.9%/year): 24 MI and 24 cardiovascular deaths.** The cohort was categorized according to tertiles of TTR values: TTR 13-58%, 59-74%, and 75-100%. There was a significant increased rate of MACE across tertiles of TTR (Log-Rank test: p<0.001). On Cox proportion hazard analysis, the 2nd vs. 1st tertile of TTR (p=0.002, hazard ratio [HR] 0.347, confidence interval [CI] 95% 0.177-0.680), 3rd vs. 1st tertile of TTR (p<0.001, HR 0.164, CI 95% 0.067-0.402), age (p<0.001, HR 1.094, CI 95% 1.042-1.148), history of stroke/TIA (p=0.015, HR 2.294, CI 95% 1.172-4.490) and smoking (p=0.003, HR 3.450, CI 95% 1.532-7.769) predicted MACE.

CONCLUSION: TTR was an independent predictor of MACE in our cohort of AF patients. **Our findings suggest that a good anticoagulation control is necessary to reduce not only the risk of stroke but also that of MACE.**

KEYWORDS: atrial fibrillation, myocardial infarction, warfarin, anticoagulant drugs, cardiovascular diseases

INTRODUCTION

Non-valvular atrial fibrillation (AF) **is a frequent cardiac arrhythmia** and is known to be associated with a high risk of thromboembolic stroke[1]. A large number of AF patients have several risk factors of atherosclerosis, which accounts for an increased risk of atherosclerotic vascular complications[2]. In particular, peripheral artery disease, as assessed by ankle-brachial index, is detectable in about 20% of patients suffering from AF[3]. Furthermore, AF patients are also at higher risk of experiencing myocardial infarction (MI)[2, 4], with a risk ranging between 0.5% to 4%/year[4]. In a population-cohort study which included 1631 participants with AF, followed up for a median period of 4.5 years, the age-adjusted incidence rate of MI was 1.2 per 100 person-years, which was significantly higher compared to patients without AF, even after adjustment for traditional atherosclerotic risk factors and potential confounders[2]. Also, in a cohort of 1019 elderly AF patients we found a high rate of MI/vascular death (3,4%/year) during the follow-up[5].

Vitamin K antagonists (VKAs) are commonly used in heart disease[6], and in patients with AF to prevent ischemic stroke with an approximately risk reduction of 64%, and a reduction in all-cause mortality by 26%[7]. While previous studies consistently showed that warfarin decreases the risk of recurrent MI in patients who had suffered from acute coronary syndrome[8, 9], its effect on MI in AF is less clear. In a prospective cohort of AF patients without a clinical history of coronary heart disease, warfarin users had a 24% risk reduction of MI, compared to non-users, but the interplay between coagulation control and MI was unclear[2]. A retrospective analysis from SPORTIF III and V[10] trials showed that good anticoagulation control was associated with a significant reduction of MI in AF patients. Amongst warfarin treated patients (n>6,000) in the RE-LY trial, well controlled VKA with Time in Therapeutic Range (TTR) ≥65% was associated with a lower MI rate compared to those patients with a TTR<65%[11].

However, the impact of warfarin on MI and other cardiovascular events in the 'real world' of AF is less certain. We therefore investigated the impact of anticoagulation quality, as assessed by TTR[12], on Major Adverse Cardiovascular Events (MACE) in a prospective study of AF patients.

Methods

Study design

This prospective single-center study included **627** patients with non-valvular AF who referred to our center for monitoring and management of antithrombotic therapies of the Department of Internal Medicine and Medical Specialties of Sapienza-University of Rome. All patients were treated with vitamin K antagonists, initially according to $CHADS_2$ score, and afterwards according to the CHA_2DS_2-VASc score[13]. Target INR value was 2.5 (range 2.0–3.0) and Time in Therapeutic Range (TTR) was used to assess the quality of anticoagulation[12]. TTR was calculated with the method described by Rosendaal[12], which uses linear interpolation of INR values to assign to each follow-up day a value of INR. Then, the percentage of days that the INR was in the therapeutic was calculated for each patient.

Exclusion criteria were patients with prosthetic heart valves, severe valvulopathies, severe cognitive impairment, chronic infections (Human Immunodeficiency Virus infection, viral hepatitis), autoimmune systemic disease, active cancer and liver insufficiency (eg, cirrhosis).

Twelve patients were lost to follow-up (10 cancer, 1 hepatic cirrhosis, 1 valve replacement). At baseline, each patient provided written informed consent and patient's anthropometric data and medical history were recorded. Cardiovascular risk factors, such as arterial hypertension[14], diabetes mellitus[15] and heart failure[16] were defined according to currently used international definitions.

Endpoints

The primary outcome of the study was a combined endpoint of major adverse cardiovascular events (MACE) including fatal/nonfatal MI and cardiovascular death. Diagnosis of MI was made according to the European Society of Cardiology definition[17]. If a patient died within 4 weeks of MI, this event was recorded as fatal MI. Death was classified as vascular unless the central adjudication committee confirmed an unequivocal non-cardiovascular cause of death. Cardiovascular death included sudden death; progressive congestive heart failure; procedure related death. Only the first event that occurred during follow-up was used in the analysis. Moreover, the occurrence of ischemic stroke or transient ischemic attack (TIA) was recorded. Ischemic stroke was diagnosed on clinical manifestations and confirmed by radiological findings, and TIA was defined according to the Classification of Cerebrovascular Diseases III.[18]

We also registered the occurrence of hemorrhages during follow-up which were classified according to the **International Society of Thrombosis And Hemostasis** definition[19].

Adjudication of events during follow-up

Data on events were prospectively collected during follow-up. When an event occurred, a standardized form was filled in by the investigators. Details on events were registered, as well as death certificates, hospital discharge letter or copy of the medical records of hospitalization, and other clinical documentation (i.e. radiology and laboratory data) were also obtained from patients, or in case of death, from relatives of patients or from general practitioner. Adjudication of cardiovascular events was performed by an internal (FV, PP) and external (FB) committee who did not participate to the recruitment of patients and was unaware of the clinical and laboratory characteristics of any enrolled patient. Each member of the committee independently evaluated and adjudicated events in a blinded manner. In case of discordant evaluation or difficult adjudication of an event, the committee decided to award the event in a collegial way. The study

protocol was approved by the local ethical board of Sapienza-University of Rome and was conducted according to principles of the Declaration of Helsinki.

Statistical analyses

Categorical variables were reported as counts (percentage), continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate. Independence of categorical variables was tested with the $\chi 2$ test. The normal distribution of parameters was assessed by Kolmogorov–Smirnov test. Student unpaired t test and Pearson product-moment correlation analyses were used for normally distributed continuous variables. Appropriate nonparametric tests (Mann-Whitney U test and Spearman rank correlation test) were used for all the other variables. Group comparisons were performed using Fisher's F-test (ANOVA) or Kruskall-Wallis test when needed. After dividing the AF population into tertiles according to TTR values, the cumulative incidence of MACE was estimated using a Kaplan–Meier product-limit estimator. Survival curves were formally compared using the log-rank test.

Cox proportional hazards analysis was used to calculate the adjusted relative hazards of MACE by each clinical variable. In the multivariable analysis, all variables (listed in table 2) have been introduced in one step (forced entry procedure). Only p values <0.05 were considered as statistically significant. All tests were two-tailed and analyses were performed using computer software packages (SPSS-18.0, SPSS Inc.).

Results

We included 627 AF patients treated with VKAs: mean age 73.3 (±8.2) years, 40.2% were women. Median follow-up was 30.8 min 3.0- max 80.0 months, yielding 1755 patients-year of observation. Clinical characteristics of all patients included in the study are summarized in table 1.

During follow-up period, we recorded 67 events. Of these, 19 (3.0%, 1.1%/year) were cerebrovascular events (stroke/TIA) and 48 (7.6%, 2.7%/year) were MACE: the latter consisted of 24 MI and 24 CV deaths. In addition, 10 cardiac revascularizations occurred (not used for the analysis), and 18 non-cardiovascular deaths related to neoplastic disease.

TTR and MACE

In the whole cohort, mean TTR was 66.8±16.6 %.We found a significant difference of mean TTR in patients with and without MACE at follow-up (56.1±17.6 vs. 67.7±16.2, respectively p<0,001). This difference was also evident in patients who experienced cerebrovascular events (57.8 ±20.8 vs. 67.1±16.4, p=0.016). Similarly, all-cause mortality was associated with a significant lower TTR (59.4±18.6 vs. 67.4±16.4 of patients free from events, p=0.003).

To investigate the relationship between TTR and MACE, we divided the cohort in three groups according to tertiles of TTR values. The first tertile of TTR included AF patients with poor anticoagulation control (n=205, median TTR: 50% [min-max 13-58]); the second tertile those with moderate anticoagulation control (n=207, median TTR: 67% [min-max 59-74]), and the third tertile those with optimal anticoagulation control group (n=215, median TTR: 83% [min-max 75-100]).

AF patients with low TTR (i.e. <60%) spent most of their time below (31.9±17.5%), than above the TTR (19.5±15.7%, p<0.001).

No differences among tertiles of TTR were found regarding clinical characteristics or concomitant therapies, with the exception of a lower prevalence of previous cardiac events in the third tertile (table 1).

Figure 1 shows the percentages of MACE for each tertile of TTR. A significantly increased incidence of MACE across tertiles of TTR **has been observed** (Log-Rank test: p<0.001), with lowest rate of MACE in patients with good anticoagulation (i.e. high TTR, Figure 2).

On multivariable Cox regression analysis, we found that age, smoking and history of stroke/TIA were positively associated to MACE, whilst second and third tertile of TTR were inversely associated to MACE (Table 2).

Similar results were obtained after the exclusion of patients with previous cardiovascular events (Tertiles of TTR: global p<0.001, HR 0.380, CI 95% 0.227-0.638).

TTR and hemorrhages

We registered 122 hemorrhages: 90 minor e 32 major, the latter consisting of 7 cerebral/subdural, 6 ocular, 9 muscular/articular, 8 gastrointestinal and 2 urinary. No differences regarding TTR were present between patients who bled or not (68.5±16.0 vs. 66.4±16.8, respectively p=0,215). Similar results were found when we considered only major hemorrhages (p=0.489).

Discussion

The principal finding in this prospective cohort study of anticoagulated AF patients was that TTR is an independent predictor of MACE. The overall rate of MACE exceeded that of stroke, and AF patients with poor anticoagulation (i.e TTR <60%) disclosed the highest incidence of MACE.

The rate of stroke/TIA of our population was similar to that reported by recent clinical trials with oral anticoagulants. Indeed, during the follow-up the annual event rate of cerebral ischemia was 1.1**%** which is consistent with previous reports showing that in AF patients treated with adjusted doses of VKAs stroke the incidence ranged from ranged from 1.1 to 4.4% per year[20].

Moreover, patients experiencing cerebrovascular events revealed a significantly lower TTR value compared to those free from events, reinforcing the need for a good anticoagulation control (such as TTR >70%) to protect patients from ischemic stroke.

The rate of cardiovascular events appears to be higher than that reported in recent interventional trials with the non-vitamin K oral anticoagulants (NOACs)[21]. Thus, the annual rate of MACE in our cohort was 2.7%, consistent with Roldàn et al.[22] who found a rate MI of 1.83%/year versus 1.66%/year of stroke; this was also consistent with a previous Italian study in high risk AF patients, which reported an annual MACE rate of 3.4%[23].

The present 'real world' study is the first to report that a good anticoagulation with VKAs is associated with a significant reduction of MACE amongst AF patients. The lowest rate of MACE was detected in AF patients with a TTR >75%, while the rate raised sharply with TTR<60%.

Our elderly AF population and atherosclerotic burden may account for this high rate of MACE. Thus, clinical history of our cohort was complicated more by coronary than cerebrovascular disease; indeed, we found that at least one atherosclerotic risk factor was detected in approximately 90% of patients.

Another possibility may be related to the different impact of VKAs on the pathophysiology of stroke and coronary events, which are largely dependent upon clotting or platelet activation, respectively[24]. Thus, it is possible that VKAs, which are able to reduce significantly thromboembolic stroke, would less favorably affect vascular events of athero-thrombotic origin, such as acute coronary syndromes. This was also evident from the results of a recent Cochrane analysis[25], including eight randomized trials and 9598 AF patients that showed how VKA significantly reduced the rate of ischemic stroke, but had less favorable effect in lowering the rate of myocardial infarction[25].

In contrast with previous findings[10], we found no association between TTR value and the occurrence of bleeding. The relative small number of major hemorrhages may account for this different result.

What are the clinical implications? Maintaining AF in good anticoagulation, is a fundamental objective to reduce not only the risk of thrombo-embolic related vascular events, but also the incidence of MACE, so reinforcing the need for a more appropriate and constant monitoring of anticoagulation in AF. The overall high rate of MACE in the real world of AF patients treated with VKAs indicates that oral anticoagulants alone may not counteract sufficiently outcomes from coronary origin, and other anti-atherosclerotic regimens should be considered to further reduce the risk of MACE. This is even more important considering that, despite the study was conducted in a specialized center for the monitoring of anti-thrombotic therapies, about one third of AF patients still had an inadequate TTR; this is in keeping with a previous finding reporting difficulty in achieving and maintaining adequate adherence to therapy with warfarin and a constant and effective anticoagulation in AF[26]. Finally, it remains to be established if the rate of MACE may be differently affected by NOACs.

Limitations. This study is limited by its observational cohort design and residual confounding is likely, although we have attempted to adjust for comorbidities on multivariate analysis. Our data refer to an elderly AF population with multiple atherosclerotic risk factors and a clinical history often complicated by coronary heart disease and, thereby, cannot be extrapolated to a younger AF population. Moreover, all patients were recruited from a single center.

Conclusions. We found that TTR was an independent predictor of MACE in our cohort of AF patients, **suggesting that a good anticoagulation control is necessary to reduce not only the risk of stroke but also that of MACE.**

Authorship

D. Pastori, P. Pignatelli, F. Violi contributed to the concept and design of the study, analysis and interpretation of data and writing of the manuscript; M. Saliola: data collection, R. Carnevale: data collection, critical writing or revising of the manuscript, T. Vicario: data collection, R. Cangemi: analysis and interpretation of data, M. Del Ben: critical writing or revising of the manuscript, F. Barillà: critical writing or revising of the manuscript, G. Y. H. Lip: critical writing or revising the intellectual content. All authors have read and approved the final version of the manuscript to be published.

Table 1. Baseline characteristics of whole cohort and according to tertiles of Time in Therapeutic Range (TTR).

	Overall	Tertiles of TTR			p value
		1st *13-58%*	2nd *59-74%*	3rd *75-100%*	
Age (years)	73.3±8.2	72.9±8.7	73.1±7.9	73.9±8.0	0.365
Persistent/Permanent AF	54.2	51.7	57.0	54.0	0.556
Women (%)	40.2	39.5	39.1	41.9	0.825
Body Mass Index (kg/m^2)	27.4±4.4	27.5±4.7	27.4±4.6	27.2±4.0	0.832
Smoking (%)	8.1	8.3	9.7	6.5	0.494
CHA_2DS_2-VASc score	3.0 [2.0-4.0]	4.0 [2.5-5.0]	4.0 [2.0-4.0]	3.0 [2.0-4.0]	0.247
Hypertension (treated, %)	94.7	91.7	96.6	95.8	0.057
Diabetes mellitus (%)	20.6	23.9	19.8	18.1	0.326
History of MI/cardiac revascularization (%)	22.3	26.8	25.1	15.3	0.009
Heart failure (%)	15.3	17.6	14.5	14.0	0.545
History of stroke/TIA (%)	14.2	17.1	15.0	10.7	0.142
Antiplatelet (%)	10.2	11.2	13.0	6.5	0.063
Statins (%)	47.2	49.8	47.3	44.7	0.577

ACE: Angiotensin Converting Enzyme, AF: Atrial Fibrillation, ARBs: Angiotensin Receptor Blockers, MI: Myocardial Infarction, TIA: Transient Ischemic Attack, TTR: Time in Therapeutic Range

Table 2. Cox proportional hazard analysis of factors associated to Major Adverse Cardiovascular Events (MACE).

	p value	HR	CI 95.0%	
2nd vs. 1st tertile of TTR*	0.002	0.347	0.177	0.680
3rd vs. 1st tertile of TTR*	<0.001	0.164	0.067	0.402
Persistent/Permanent AF	0.744	0.906	0.500	1.641
Female sex	0.525	0.806	0.415	1.565
Age	<0.001	1.094	1.042	1.148
Hypertension (treated)	0.377	0.576	0.169	1.960
Diabetes	0.344	1.410	0.692	2.874
Heart Failure	0.106	1.753	0.887	3.463
History of Stroke/TIA	0.015	2.294	1.172	4.490
History of MI/Cardiac revascularization	0.336	1.384	0.714	2.681
Antiplatelet	0.805	0.881	0.323	2.402
Smoking	0.003	3.450	1.532	7.769
Statins	0.165	1.573	0.830	2.981

*Global p value: p<0.001.

AF: Atrial Fibrillation, CI: Confidence Interval, HR: Hazard Ratio, MI: Myocardial Infarction, TIA: Transient Ischemic Attack, TTR: Time in Therapeutic Range

Figure Legend

Figure 1. Percentages of MACE according to tertiles of time in therapeutic range.

Figure 2. Kaplan-Meier curves estimate of survival free from MACE according to tertiles of time in therapeutic range. Black line: first tertile, dark grey line: second tertile, light grey line: third tertile (Log-Rank test, p<0.001).

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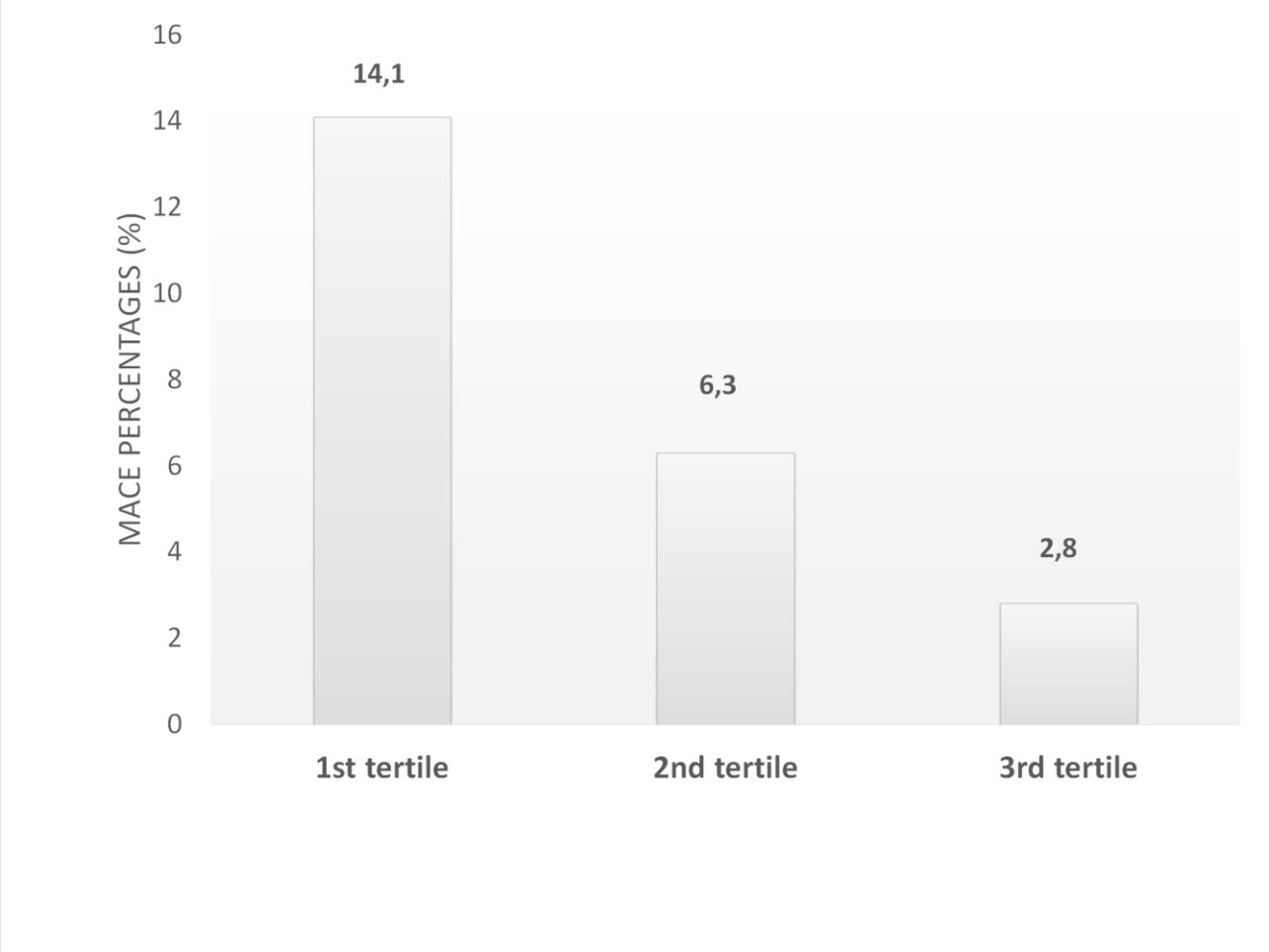

Figure 1

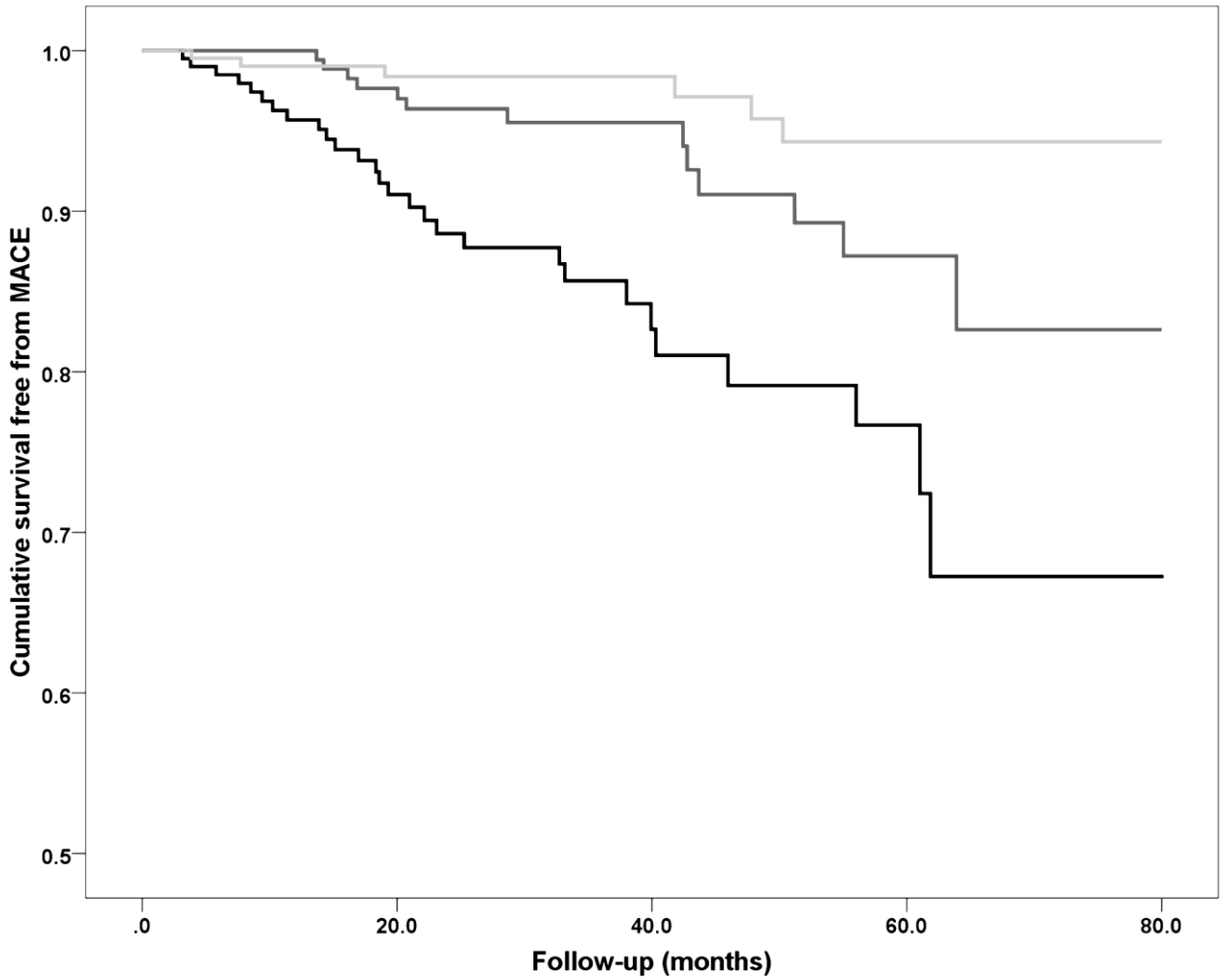

Figure 2